whereby, when the primer is immobilized via the immobilization attachment site, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

REMARKS

Any fees that are due with this paper or application can be charged to Deposit Account No. 50-1213. If a Petition for extension of time is due, this paper can be considered such Petition.

Claims 1-21 are presently pending in this application. Claim 1 is amended to more distinctly claim the subject matter by correcting an inadvertent grammatical error.

A marked up copy per 37 C.F.R. §1.121 showing changes made to the claims is attached to this response.

THE REJECTION OF CLAIMS 1-9, 11-14, 20 and 21 UNDER 35 U.S.C. §102(e)

Claims 1-9, 11-14, 20 and 21 are rejected under 35 U.S.C. § 102(e) as anticipated by Köster *et al.* (U.S. Patent 5,622,824) because Köster *et al.* allegedly discloses a nucleic acid primer having a first region containing the 5' end of the primer and an immobilization attachment site, and a second region containing the 3' end of the primer and a chemically cleavable site, where the 3' end is capable of being extended by an enzyme. It is further alleged that the limitations of dependent claims 2-9, 11-14, 20 and 21 are inherent in the disclosure of Köster *et al.* and thus the disclosure of Köster *et al.* allegedly "anticipates the limitations" of claims 1-9, 11-14, 20 and 21." This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9

USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Independent claim 1 and its dependent claims (2-21) are directed to a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a *chemically* cleavable site. The 3' end is capable of being extended by an enzyme to generate an extension segment. When the primer is immobilized via the immobilization attachment site, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

DIFFERENCES BETWEEN THE CLAIMS AND THE TEACHINGS OF THE CITED REFERENCE

Köster *et al.* (5,622,824)

Köster *et al.* discloses a method of determining the sequence of a nucleic acid by enzymatic sequential directed digestion of the nucleic acid by exonucleases and identification of the sequentially released fragments using mass spectrometry (MS). The reference discloses the use of MALDI-TOF MS for analysis of biomolecules, using PCR methods to amplify test material, and use of exonucleases and mass-modified nucleoside triphosphates to modify the sample biomolecule prior to analysis. Köster discloses attaching a linear single-stranded

DNA fragment to a solid support via its 5' end and attaching a target DNA to be sequenced via a "splint oligonucleotide" containing sequences complementary to the bound DNA fragment and the DNA fragment to be sequenced. Köster discloses releasing nucleotides from the 3' end of the target DNA by contacting it with a 3'-exonuclease which digests the nucleotides. As demonstrated below, Köster does not disclose primers where the 3' end contains a chemically cleavable site; the nucleic acid molecules are enzymatically and sequentially digested in the method of Köster.

ANALYSIS

Köster does not anticipate any of the instant claims, because Köster does not disclose primers with a 3' end that includes a chemically cleavable site.

Claim 1 is directed to a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a chemically cleavable site. The basis for rejection appears to be that the 3' end of the primer disclosed in Köster allegedly is "chemically cleavable" because Köster discloses degradation of the 3' end using a 3' exonuclease. Thus, the basis for the rejection appears to be that the 3' end of the primer, being cleavable by 3' exonuclease degradation, is allegedly an example of a "chemically cleavable" site.

It is respectfully submitted that an enzymatic digestion from the 3' end is not chemical cleavage. Thus, the term "chemically cleavable," as used in the specification and understood by those of ordinary skill in the art does not encompass enzymatic digestion.

The term "chemically cleavable site" is used throughout the specification to describe specific sites that are cleaved as a result of a non-enzymatic chemical reagent. For example, the specification, at page 7, lines 1-6, teaches that a chemically cleavable site can be "modified based, a modified sugar, or a chemically cleavable group incorporated into the phosphate backbone of the

primer" and provides examples of a chemically cleavable site. In contrast, the following paragraph at page 7, line 7, teaches other cleavable sites that "include nucleotides cleavable by an enzyme such as a nuclease." Thus, the specification distinguishes chemically cleavable sites from enzymatically cleavable sites.

The specification provides a large number of examples of chemically cleavable sites. For example, at page 38, lines 18-27 and Figure 1, the specification lists chemically cleavable sites including: dialkoxysilane, β-cyano ether, 5'-deoxy-5'-aminocarbamate, 3'deoxy-3'aminocarbamate, urea, 2'cyano-3',5'-phosphodiester, 3'-(S)-phosphorothioate, 5'-(S)-phosphorothioate, 3'-(N)-phosphoramidate, 5'-(N)-phosphoramidate, α-amino amide, vicinal diol, ribonucleoside insertion, 2'-amino-3',5'-phosphodiester, allylic sulfoxide, FIG. IP; ester, silyl ether, dithioacetal, 5'-thio-formal, α-hydroxy-methyl-phosphonic bisamide, acetal, 3'-thio-formal, methylphosphonate and phosphotriester.

The specification also teaches methods for cleavage of such chemically cleavable groups. For example, at page 64, lines 13-25, the specification teaches the reagents used for cleavage of such chemically cleavable groups include fluoride ion, base, silver nitrate, mercuric chloride, acid, isothiocyanate, titanium and periodate. Example 1, for example, teaches use of 80% acetic acid for selective chemical cleavage of a phosphoramidate internucleotide bond. (Page 79, lines 11-15). Additional examples of such cleavage are taught in specification, for example, at page 40, lines 22-28, which teaches cleavage of dialkoxysilane using fluoride ion, and at page 42, lines 4-7, which teaches cleavage of phosphorothioate using silver nitrate.

In addition, the specification clearly distinguishes between chemical and enzymatic reactions. For example, at page 11, lines 10-11, and page 45, lines 12-14, the specification states that digestion can be chemical or enzymatic digestion; and at page 28, lines 5-6, the specification states that attachment can be accomplished by chemical or enzymatic means.

Furthermore, those of ordinary skill in this art distinguish between chemical and enzymatic cleavage. For example, Köster 5,547,835 (cited by the Office in the rejection under 35 U.S.C. §103 in this Action), discussed belowm, distinguishes between chemical and enzymatic cleavage. For example, Köster states with reference to removal of oligonuculeotides from solid supports that:

> In one embodiment of the invention, the linking chemistry allows one to cleave off the so-purified nested DNA enzymatically, chemically or physically. By way of example, the L--L' chemistry can be of a type of disulfide bond (chemically cleavable, for example, by mercaptoethanol or dithioerythrol), a biotin/streptavidin system, a heterobifunctional derivative of a trityl ether group (Koster et al., "A Versatile Acid-Labile Linker for Modification of Synthetic Biomolecules," Tetrahedron Letters 31, 7095 (1990)) which can be cleaved under mildly acidic conditions, a levulinyl group cleavable under almost neutral conditions with a hydrazinium/acetate buffer, an arginine-arginine or lysine-lysine bond cleavable by an endopeptidase enzyme like trypsin or a pyrophosphate bond cleavable by a pyrophosphatase, a photocleavable bond which can be, for example, physically cleaved and the like (see, e.g., FIG. 23). Optionally, another cation exchange can be performed prior to mass spectrometric analysis. In the instance that an enzyme-cleavable bond is utilized to immobilize the nested fragments, the enzyme used to cleave the bond can serve as an internal mass standard during MS analysis.

Köster continues:

> Examples of suitable metal surfaces include steel, gold, silver, aluminum, and copper. After purification, cation exchange, and/or modification of the phosphodiester backbone of the L--L' bound nested Sanger fragments, they can be cleaved off the solid support chemically, enzymatically or physically.

Thus art relied on in the Office Action, clearly distinguishes chemically, physically and enzymatically cleavable sites in oligonucleotides and distinguishes between chemical cleavage, physical cleavage and enzymatic cleavage.

In sum, those of ordinary skill in the art distinguish chemical from enzymatic cleavage, and the teachings of the instant specification distinguish a "chemically cleavable site" from a site cleavable by enzymatic means. It is clear from the specification that the term "chemically cleavable site" does not

encompass cleavable by enzymatic means, the "chemically cleavable site" of claim 1 does not encompass the 3' end of an oligonucleotide and is not anticipated by the dislosure of Köster of a 3' end that is cleavable by a 3' exonuclease. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. Köster does not disclose a nucleic acid primer having a second region at the 3' portion that includes a chemically cleavable site. Thus, the cited reference fails to disclose every element of the claimed subject matter. Accordingly, Köster does not anticipate any of claims 1-21.

THE REJECTION OF CLAIMS 15-19 UNDER 35 U.S.C. §103(a)

Claims 15-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,622,824) in view of Köster (U.S. Patent 5,547,835) because Köster '824 allegedly teaches every element of the claimed subject matter except that the solid support includes a functionality selected from among avidin and streptavidin, and antibody and anti-antibody, but the Examiner alleges that Köster '835 cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining

the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

THE CLAIMS

Dependent claims 15-19 are directed to various embodiments of the primer of independent claim 1. For example, claim 15 is directed to a primer that includes a solid support, where the solid support includes a functionality selected from avidin and streptavidin. Claim 16 is directed to a primer that includes a solid support, where the solid support includes an antibody. Claim 17 depends from claim 16 and is directed to a primer where the antibody includes anti-digoxigenin. Claim 18 is directed to the primer of claim 1 where the immobilization attachment site is a substituent on one of the bases or sugars

of the primer. Claim 19 is directed to the primer of claim 1 where the immobilization attachment site is biotin or digoxigenin.

Differences between the cited references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above. As discussed above, Köster fails to disclose or teach a primer with a 3' end with a chemically cleavable site.

Köster (U.S. Patent 5,547,835)

Köster '835 is directed to a mass spectrometric method for sequencing using a Sanger sequencing strategy, in which one embodiment includes immobilizing the sequencing primers to a support using various linkers. Köster '835 teaches that the primer has a linking functionality L at the 5'-end that interacts with a suitable functionality L' on the solid support to form a reversible linkage L-L' (col. 11, lines 52-56).

As discussed above, Köster '835, distinguishes among chemical, enzymatic and physical cleavage. For example, Köster states:

> By way of example, the L--L' chemistry can be of a type of disulfide bond (chemically cleavable, for example, by mercaptoethanol or dithioerythrol), a biotin/streptavidin system, a heterobifunctional derivative of a trityl ether group (Koster et al., "A Versatile Acid-Labile Linker for Modification of Synthetic Biomolecules,"Tetrahedron Letters 31, 7095 (1990)) which can be cleaved under mildly acidic conditions, a levulinyl group cleavable under almost neutral conditions with a hydrazinium/acetate buffer, an arginine-arginine or lysine-lysine bond cleavable by an endopeptidase enzyme like trypsin or a pyrophosphate bond cleavable by a pyrophosphatase, a photocleavable bond which can be, for example, physically cleaved and the like (see, e.g., FIG. 23).

Thus, Köster '835 not only does not cure the deficiencies in the teachings of Köster '824, it teaches that chemical and enzymatic cleavage are distinct.

ANALYSIS

The claims are not *prima facie* obvious because the combination of teachings of Köster '824 with the teachings of Köster '835 does not result in the instantly claimed primers.

Claims 15-19 of the instant application are directed to various embodiments of the nucleic acid primer of claim 1. As discussed above, Köster '824 does not teach or suggest a nucleic acid primer that has a 5' portion, and 3' portion that includes a chemically cleavable site. Köster '835 does not cure these defects. Köster '835 teaches a nucleic acid primer that has a 5' end containing a linking functionality L, which can interact with a suitable functionality L' on a solid support to form a temporary reversible linkage, and a 3' end that is base-specifically terminated (col. 11, lines 52-56; Figure 1). This can be depicted as:

SS—L'-L—5'————————————————————3'—T.

Köster '835 does not teach or suggest a nucleic acid primer containing a second region containing the 3' end of the primer and a chemically cleavable site, such that when the primer is immobilized, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Instead, Köster '835 teaches a cleavable L—L' linkage at the 5' end of the nucleic acid primer, cleavage of which removes the entire primer from the solid support (column 11, line 52 - column 13, line 2). The only chemically cleavable site taught or suggested by Köster '835 is the chemically cleavable site at the 5' end of the primer. Hence, Köster '835 fails to teach a second region of a primer containing the 3' end and a chemically cleavable site.

Since, Köster '835 fails to teach a second region of a primer containing the 3' end and a chemically cleavable site, Köster '835 fails to cure the deficiencies in the teachings of Köster '824. The combination of teachings of Köster '824 and Köster '835 fails to result in the instantly claimed primers. The combination of the teachings of Köster '824 and Köster '835 does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a unique chemically cleavable site and a 3' end that is capable of being extended by an

enzyme to generate an extension segment. Therefore, the Office Action does not set forth a *prima facie* case of obviousness, and the rejection should be withdrawn.

THE REJECTION OF CLAIM 10 UNDER 35 U.S.C. §103(a)

Claim 10 is rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,662,824) in view of Richards *et al.* (U.S. Patent 5,427,929) because Köster allegedly teaches every element of claims 1-9, 11-14, and 20-21, and although Köster does not teach the ligase enzyme of claim 10, the Examiner alleges that Richards *et al.* cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 10 depends from claim 1 and is directed to the primer of claim 1, 3' end is capable of being extended by a ligase.

Differences between the cited references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above.

Richards *et al.* (U.S. Patent 5,427,929)

Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure by incorporating at least one modification into the amplification product to distinguish it from the target sequence and allow it to be identified as background contamination. The reference teaches including restriction endonuclease target sites as cleavable sites in the amplification products, and use of restriction endonucleases to cleave the resulting modified products (see, e.g., Figures 5-9, 12-15, and 19). Prior to further amplification, the sample is treated to selectively cleave the contaminant amplification product so that it cannot be amplified in the new sample. The reference teaches a method of using ribonucleotide substitution at the 3'-end of an amplification

product and then extending it using PCR or LCR so that the ribonucleotide substitution is internalized in the sequence (col. 17, lines 33-45 and line 65 through col. 18, line 13). Richards *et al.* teaches that it is preferred to locate the chemically cleavable site modification near the middle of an amplification probe or primer so that disruption of hybridization will be minimized (col. 17, lines 19-22). Richards *et al.* teaches the introduction of a number of different types of modifications into the amplification product (col. 9, lines 24-27) and the number of modification sites incorporated into the amplification product may vary (col. 10, lines 7-10). Richards *et al.* teaches that the amplification product can be modified at or about any location other than the extending end of the primer that does not interfere with amplification, and in that case the modification should be modified at its 5' end (col. 11, lines 15-30).

Richards *et al.* does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, including a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a chemically cleavable site.

ANALYSIS

The claims are not *prima facie* obvious because the combination of teachings of Köster '824 with the teachings of Richards does not result in the instantly claimed primers.

As discussed above, Köster '824 does not teach or suggest a nucleic acid primer that has a 5' portion, and 3' portion that includes a chemically cleavable site. Richards, which does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, including a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a chemically cleavable site, does not cure these defects.

Notwithstanding the above, there would have been no motivation to combine the teachings of Köster with those of Richards *et al.*

The Examiner contends that one of ordinary skill in the art at the time of the instant application would have been motivated to "use a ligase in a nucleic

acid polymerization reaction as taught by Richards *et al.* because the method of Richards *et al.* is efficient and economy [*sic*] for reducing carryover contamination in an amplification procedure" (citing the Abstract).

Richards *et al.* teaches that it is preferred to incorporate modifications site(s) into the nucleic acid at locations "which, when cleaved, will result in the most complete destruction of the" nucleic acid. (Column 12, line 66, through column 13, line 3). The purpose of the cleavable sites in Richards *et al.* is to assist in the degradation and elimination of the nucleic acids that contain the cleavable sites because these nucleic acids are seen as contaminants. (Abstract). Thus, the teachings of Richards *et al.* are directed toward eliminating as contaminants the nucleic acids containing cleavable sites.

In considering the prior art under 35 U.S.C. 103, the totality of the prior art must be considered. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Köster is directed to nucleic acid sequencing methods using mass spectrometry. A method of sequencing a nucleic acid is not improved by eliminating that nucleic acid as a contaminant, regardless of whether or not the method of eliminating that contaminant is more economical or efficient. Thus, one skilled in the art seeking to sequence a nucleic acid would not be motivated to modify that nucleic acid according to the teachings of economically and efficiently eliminating nucleic acids as contaminants. Accordingly, one skilled in the art seeking to modify the teachings of Köster would not be motivated to modify the nucleotide sequenced according to the method of Köster with the economic and efficient contaminant elimination method of Richards *et al.* to form a primer.

"Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." *In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (emphasis original). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the

modification." *In re Fritch*, at 1783-84. Without the teachings of the prior art suggesting the combination, it is impermissible to pick and choose among isolated disclosures in the prior art to conclude that the claimed in subject matter is obvious. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Köster does not suggest that a nucleic acid to be sequenced should be modified in order for the nucleic acid to be more efficiently eliminated as a contaminant. Richards *et al.* does not suggest use of the method of eliminating contaminant nucleic acids in order to determine the sequence of the contaminant nucleic acid. Thus, neither of the cited references suggests combining the teachings of Köster with the teachings of Richards *et al.* in forming the nucleic acid of claim 10. Without the teachings of the references suggesting the combination, it is impermissible to pick and choose from Köster and Richards *et al.*
to conclude that the claimed primers are obvious. Accordingly, the Office Action has not set forth a *prima facie* case of obviousness of claim 10.

* * *

In view of the above remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Monforte *et al.*

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Michael Lough

MARKED UP CLAIMS IN ACCORDANCE WITH 37 C.F.R. § 1.121

Please amend claim 1 as follows:

1. (Amended) A nucleic acid primer having a 5′ end and a 3′ end, comprising:

(a) a first region containing the 5′ end of the primer and an immobilization attachment site; and

(b) a second region containing the 3′ end of the primer[, wherein the 3′ end is capable of being extended by an enzyme to generate an extension segment,] and a chemically cleavable site, <u>wherein the 3′ end is capable of being extended by an enzyme to generate an extension segment</u>,

whereby, when the primer is immobilized via the immobilization attachment site, and the chemically cleavable site is cleaved, the remainder of the primer remains immobilized.